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Short title: Polyandry and selfish genetic elements

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Abstract

Segregation distorters located on sex chromosomes are predicted to sweep to fixation and cause extinction via a shortage of one sex, but in nature they are often found at low, stable frequencies. One potential resolution to this long-standing puzzle involves female multiple mating (polyandry). Because many meiotic drivers severely reduce the sperm competitive ability of their male carriers, females are predicted to evolve more frequent polyandry and thereby promote sperm competition when a meiotic driver invades. Consequently, the driving chromosome's relative fitness should decline, halting or reversing its spread. We used formal modeling to show that this initially appealing hypothesis cannot resolve the puzzle alone: other selective pressures (e.g. low fitness of drive homozygotes) are required to establish a stable meiotic drive polymorphism. However, polyandry and meiotic drive can strongly affect one another's frequency, and polyandrous populations may be resistant to the invasion of rare drive mutants.

Introduction

Selfish genetic elements subvert normal patterns of DNA replication in ways that increase their representation in subsequent generations, often at the expense of the fitness of the rest of the genome (Burt and Trivers 2006). They are ubiquitous in living organisms, and the intragenomic conflicts they create have major impacts on the evolution of sex, genetic systems, host ecology and population dynamics (Hurst and Werren 2001; Burt and Trivers 2006; Charlat et al. 2007a; Werren 2011; Wedell 2013).

Segregation distorters, such as meiotic drivers, are selfish genetic elements that manipulate gametogenesis and thereby enhance their representation in the gametes relative to non-distorting elements (Burt and Trivers 2006). This transmission advantage is expected to cause meiotic drivers to rapidly go to fixation, assuming that

drive-bearing and non-drive-bearing individuals have equivalent survival and reproductive success (Ardlie 1998; Burt and Trivers 2006). Several species possess meiotic drivers located on an X chromosome, which is transmitted to up to 100% of the progeny of male carriers (Beckenbach 1978; James and Jaenike 1990; Presgraves et al. 1997; Ardlie and Silver 1998; Cazemajor et al. 2000; Hurst and Werren 2001; Werren 2011; Wedell 2013). These X-linked drivers can create strongly female biased population-wide sex ratios (Jaenike 2001; Burt and Trivers 2006), potentially causing extinction due to a shortage of males. Although putative population crashes caused by meiotic drive have occasionally been reported (Pinzone and Dyer 2013), meiotic drive has often been found in nature at stable, intermediate frequencies over wide geographic areas and long periods of time (Dobzhansky 1958; Huang et al. 2001; Dyer 2012). What maintains polymorphisms for meiotic drive (i.e. co-existence of driving and non-driving chromosomes or alleles) is therefore a long-standing puzzle, as is the lower-than-expected frequency of drive in some natural populations (e.g. Lewontin 1968; Charlesworth and Hartl 1978; Taylor and Jaenike 2002; Safronova and Chubykin 2013; Auclair et al. 2013).

Why don't all meiotic drivers spread to fixation? Past attempts to explain polymorphisms have mainly sought sources of negative frequency-dependent selection on drive-carrying individuals. Under negative frequency-dependent selection, a meiotic driver might spread when at low frequencies because of its transmission advantage in segregation, and decline at high frequencies because of the reduced fitness of its bearers. Low fitness of meiotic drive homozygotes is one possible source of negative frequency-dependent selection, because drive homozygotes increase in frequency as the driver becomes more common. Accordingly, several meiotic drivers, including the *t* haplotype of mice (Ardlie 1998) and meiotic drive in some *Drosophila* (Dyer et al. 2007;

Larracuente and Presgraves 2012), cause sterility, death or milder deleterious effects in homozygotes. These effects might arise because genomic regions near meiotic drivers often undergo little or no recombination (Silver and Artzt 1981; Dyer et al. 2007; Larracuente and Presgraves 2012), allowing the buildup of deleterious genetic material at sites linked to the driver. However, meiotic drive homozygotes appear to have comparable fitness in some systems (Powell 1997; Price et al. 2012a). Costs to homozygotes are therefore likely to be only part of the answer, especially since meiotic drive is often found at even lower frequencies than predicted under homozygote lethality or sterility (the so-called "*t*-paradox"; Lewontin 1968; Ardlie and Silver 1998; Manser et al. 2011).

Taylor and Jaenike (2002; 2003) modeled another solution, based on observations that drive-carrying males experience an especially severe decline in their ability to fertilize females and outcompete other males' sperm after mating a number of times (Wu 1983; Jaenike 1996; Pinzone and Dyer 2013). This hypothesis is appealing because there is abundant evidence that drive-carrying males are disadvantaged in sperm competition relative to non-carrier males, often because their Y-bearing sperm fail to develop (e.g. Wilkinson and Fry 2001; Atlan et al. 2004; Wilkinson et al. 2006; Angelard et al. 2008; Price and Wedell 2008; Price et al. 2008a; Manser et al. 2011). Male mating rate is expected to increase as the driving X (and hence females) becomes more common, so the comparatively poor ability of drive-carrying males to fertilize multiple females might impose negative frequency-dependent selection on meiotic drive. However, Taylor and Jaenike (2002; 2003) also noted that sperm competition will generally become less frequent as the sex ratio shifts towards females, because fewer females will encounter multiple potential mates. This should impose *positive* frequency-dependent selection on drive, because the growing rarity of female multiple mating

should increase the relative fitness of the driving X as it invades. Because of these conflicting effects of population-wide sex ratio on drive males' fitness, polyandry only prevented the fixation of drive in a limited set of conditions in Taylor and Jaenike's model, making it unclear whether impaired spermatogenesis in drive males is a general resolution to the current problem.

Recent data suggest another potential source of negative frequency-dependent selection arising from sperm competition, which relies on female evolutionary responses to the presence of drive-carrying males (Wedell 2013). When drive males are disadvantaged in sperm competition, females can reduce the proportion of their eggs that are fertilized by meiotic drive males by mating with multiple males (Haig and Bergstrom 1995; Wilkinson and Fry 2001; Price et al. 2010; Manser et al. 2011). An experimental evolution study found that females indeed evolved higher frequencies of multiple mating when a meiotic driver that negatively affects sperm competitive ability in male carriers was introduced into the population (Price et al. 2008b). Moreover, geographical clines in the frequency of X-linked meiotic drivers in North American populations of *Drosophila pseudoobscura* and *D. neotestacea* correlate with the local frequency of female multiple mating (Pinzone and Dyer 2013; Price et al. 2014). Together with abundant evidence that polyandry can rapidly respond to selection (e.g. Harano and Miyatake 2007; Price et al. 2008b), this correlation is consistent with coevolution between polyandry and meiotic drive in the wild.

It is not straightforward to assess whether coevolution between polyandry and meiotic drive provides a sufficiently strong source of negative frequency-dependent selection to prevent the fixation of meiotic drive. Intuitively, as the meiotic driver increases in frequency in a population due to its transmission advantage, females might evolve to be more polyandrous, causing the driver to go into decline due to its

disadvantage in sperm competition. As the meiotic driver falls in frequency, females might evolve lower polyandry, since multiple mating often has costs (e.g. Wigby and Chapman 2005) and therefore should provide weaker net fitness returns when drive-bearing males are scarce. Whether these coevolutionary dynamics are able to protect genetic polymorphism for driving X chromosomes is difficult to predict without formal modeling. To address these questions, we used genetically explicit models to examine the potential for (and evolutionary consequences of) coevolution between polyandry and driving X chromosomes. Model 1 is analytical and hence can be investigated more thoroughly, but it makes several simplifying assumptions. These assumptions are relaxed in Model 2, which is a stochastic individual-based simulation.

Model 1: A deterministic simulation

We consider a panmictic population composed of two sexes with XX/XY sex determination and non-overlapping generations. The population contains non-driving X chromosomes, driving X chromosomes and Y chromosomes, which we denote X, X* and Y respectively. XY males have fair meiosis, but X*Y males transmit an X* chromosome with probability $(1 + d)/2$ and a Y with probability $(1 - d)/2$. Therefore, $d = 0$ denotes even segregation of sex chromosomes in X*Y males, and $d = 1$ complete meiotic drive ($0 \leq d \leq 1$). When $d = 1$, all eggs fertilized by X*Y males develop into females.

To be able to derive analytical expressions for the evolving frequency of polyandrous or monandrous females, we assume the simplest possible genetic control of polyandry: a single, haploid autosomal locus with two alleles A and a. We assume random mating, and that females mate either once or twice depending on whether they carry allele A or a respectively. Males carry the A/a locus but do not express it. Since there are two possible genotypes at the A/a locus and five sex chromosomes genotypes

(XX, X*X and X*X* females, plus XY and X*Y males), the model must track ten genotypes. The assumption of haploidy at the A/a locus is artificial but greatly simplifies the model, and is unlikely to affect its qualitative conclusions; this assumption is relaxed in Model 2 below.

We further assume that polyandrous females (those carrying the A allele) pay a fecundity cost such that their fecundity is multiplied by $1 - p$, where $0 \leq p \leq 1$. The parameter p represents the costs to females of mating multiply (e.g. due to extra mate search costs or additional harm from contact with males). We also implemented a fecundity cost h ($0 \leq h \leq 1$) to females with the genotype X*X*, in order to investigate the joint evolutionary consequences of polyandry and homozygote disadvantage. Females with the genotype aX*X* thus have fecundity $1 - h$ and those with the genotype AX*X* have fecundity $(1 - p)(1 - h)$; that is, we assume multiplicative fitness costs of polyandry and X* homozygosity. All other female genotypes had a fecundity of 1 or $1 - p$, depending on whether they carried the a or A allele respectively.

Tracking offspring genotypes

For singly mating females, the expected frequency of each type of offspring can be readily predicted from the parental genotypes, assuming random mating, Mendelian segregation in females and XY males, and biased segregation in X*Y males (when $d > 0$). For example, fertilizations of the eggs of an aXX female by an AX*Y male produce aX*X and AX*X daughters with frequency $(1 + d)/4$ each, and aXY and AXY sons with frequency $(1 - d)/4$ each. Other frequencies are derived analogously. Our assumption of random mating follows the finding that drive-carrying males often appear to have equivalent mating success (e.g. Price and Wedell 2008; Price et al. 2012b).

The expected genotypes of the offspring of twice-mated females also depend on the outcome of sperm competition. The frequency of a given type of "mating trio" equals $2fm_1m_2$, where f, m_1 and m_2 refer to the genotype frequencies of the female and her two mates. We assume that males of different genotypes are equally likely to mate in the first male or second male roles, meaning that sperm precedence effects (Parker et al. 1990) are inconsequential for our model. There are 3 polyandrous female genotypes and 4 male genotypes, so we must track 30 possible mating trios.

Paternity is shared equally when both males are XY or both are X*Y. However when one male is XY and the other is X*Y, the XY male sires a proportion $1/(1 + c)$ of the offspring and the X*Y males sires the remaining $c/(1 + c)$. The parameter c $(0 \leq c \leq 1)$ thus measures the relative competitiveness of X*Y males in sperm competition (averaged across the first and last male roles): $c = 0$ means X*Y males gain no offspring if the female has also mated with an XY male, and $c = 1$ means X*Y and XY males share paternity equally when they mate with the same female.

Model 1 also assumes that monandrous females always mate once, and polyandrous females always mate twice, irrespective of the population sex ratio. Although potentially unrealistic, this assumption is important if Model 1 is to exclude the sources of frequency dependent selection modeled by Taylor and Jaenike (2002); this assumption is relaxed in Model 2. Because we assume no sperm limitation and an invariant number of mates per female for all frequencies of X*, any instances of X chromosome polymorphism in Model 1 must result from distinct evolutionary processes to those previously studied.

Although the model yields analytical expressions for the frequencies of each genotype from one generation to the next, the solutions are very complex. We therefore determined equilibrium gene frequencies numerically, by iteratively determining the predicted offspring genotype frequencies from the parental ones given the model's four global parameters: d, c, p and h. Each generation, we normalized offspring genotype frequencies to sum to unity by dividing them by the sum of the frequencies. The model therefore assumes a large population in which genetic drift is negligible (this assumption is relaxed in Model 2).

Note that although Model 1 does not include mate or sperm limitation (i.e. all females were assumed to be fully fertile even when males were rare; this assumption is removed in Model 2), the output of the model can be interpreted such that parameter spaces that drastically reduce the frequency of males would likely result in extinction in the real world.

Model 2: A stochastic simulation

Model 1 has a number of limitations. For simplicity, it assumed haploid inheritance at the polyandry locus, infinite population size (negating genetic drift), discrete time, and that mating and fertilization occur just as efficiently when males are scare. To relax these assumptions and verify the generality of Model 1's conclusions, we constructed an individual-based stochastic simulation in continuous time, termed Model 2. Model 2 uses the Gillespie algorithm, which allows us to model discrete stochastic events (e.g. matings, deaths) that occur at different rates in continuous time, by considering the exponentially distributed time it takes for a next event to occur, as well as events that occur after a fixed time has elapsed (e.g. maturation). For details of the algorithm see Kokko and Heubel (2011). The life cycle proceeds as follows.

Individuals carry two diploid loci: the A/a female mating behavior locus, and sex chromosomes, which can be X, X* or Y. In half the simulations, we assumed that the polyandry allele A is dominant; in the other half it was recessive. Individuals begin life as pre-reproductive individuals (this includes eggs and larvae), which become mature adults if they survive for 0.05 time units. Adults of both sexes live for one time unit and then die. Pre-reproductive individuals die in a density-dependent fashion: the rate of deaths in the pre-reproductive population is $(N_e)^3/10^4$ where N_e is the number of pre-reproductive individuals. Density-dependent egg-to-adult survival thus limits population growth in the model.

The mating rate of a female who is available to mate (i.e. is mature, but has not yet reached her maximum number of matings) is mN_m, where m is a constant determining the mating rate and N_m is the number of males in the population. Matings occur one at a time, and a female is immediately categorized as no longer available to mate if she has reached her maximum number of matings, which is one mating for aa females, two matings for AA females, and either one or two for Aa females depending on the dominance of allele A. Note that by "mating rate", we always mean the rate at which matings occur, not the total number of matings per female.

Males that have mated become sperm depleted, modeled by instantaneously setting the focal male's "sperm depletedness" (s_i) to one (s = 0 for virgin males). Sperm depletedness then declines exponentially towards zero at rate r over time: thus if a non-virgin male mates 0.5613 time units after his previous mating, his depletedness at the time of the new mating is $\exp(-0.5613r)$. Note that a male is not less likely to mate if he has few sperm available: we assume that males mate at every opportunity and that females cannot discriminate among males with varying sperm stores. In order to exclude the source of negative frequency-dependent selection proposed by Taylor and

Jaenike (2002; 2003) and limit the number of parameters in the model, we assumed that the sperm replenishment rate was the same for XY and X*Y males.

Mated females lay all their eggs immediately before their death if they acquired one or two matings during their lifetime, and unmated females die without leaving offspring. Thus, when males are rare and/or m is low, many potentially polyandrous females will mate only once before reproducing, and females of any genotype may also die without mating at all.

The maximum possible number of eggs produced is f (f = 10 in all simulations). In Model 2, three processes can reduce female fecundity from this maximum value. First, f is multiplied by $(1 - p)$ for females that mated twice (the cost of polyandry), and second, by $(1 - h)$ for X*X* females (the cost of homozygous drive chromosomes; double-mated X*X* females pay both costs) just as in Model 1. Third, female fecundity can fall lower still because of sperm limitation. The fecundity of singly mated females depends on their mate's sperm-depletedness (s_i) at the time of mating. Fecundity is multiplied by $(1 - s_i)^k$, where k is a constant governing the shape of the relationship between fecundity and the amount of sperm received. The fecundity of doubly-mated females is multiplied by either $(1 - s_1)^k + (1 - s_2)^k$ (where the subscripts refer to the first and second mate), or 1, whichever is lower. That is, we assume that a female mating with one virgin male reproduces at her own maximum possible fecundity (which depends on her genotype, p and h), but that females who obtain even more sperm than that of a virgin male by mating twice can equal but not exceed their maximum fecundity. We assume k = 5 in all simulations, meaning that additional sperm is especially valuable to females whose first mate was strongly sperm depleted.

The paternity of eggs laid by doubly mated females depends on sperm competition. When both males are XY or both are X*Y, the focal male has a paternity probability of $s_i/(s_i + s_j)$; that is, we assume that sperm-depleted males are worse in sperm competition. This formula is modified to $cs_i/(cs_i + s_j)$ if the focal male is X*Y and the other XY, or $s_i/(s_i + cs_j)$ if the focal male is XY and the other X*Y. The genotypes of the eggs produced are decided by Mendelian segregation, and eggs become adults 0.05 time units after being laid if they survive pre-reproductive density-dependent mortality. Note that although Model 2 could incorporate non-overlapping generations, in practice generations were discrete because we initiated the population with adults only, all of which laid eggs and died at the same time. Therefore, adults did not mate with their own offspring.

Simulations were initialized with the polyandry allele at 50% frequency and X* at either 10% or 90% frequency (allowing us to estimate its likely evolutionary endpoint in parameter spaces where evolution was very slow; see Results and Figure S8). We ran the simulation until the population went extinct, or until a total of 100,000 eggs had been produced (10 replicates per parameter space for a total of 17,280 runs).

Results of Model 1

X has trouble spreading in a fully polyandrous population*

First, we investigated whether polyandry can prevent X* from invading when all females in the population are polyandrous and when there are no costs to X* homozygotes ($h = 0$). Note also that if we had assumed that polyandry confers a net direct benefit ($p < 0$) in Model 1 rather than a cost, the polyandry allele would always increase and fix, resulting in a uniformly polyandrous population. In a population where all females mate twice, an analytical approximation exists that permits simpler

solutions than the general case, provided that we assume X* is rare (see Online Supplementary Material). In short, a rare X* mutant can invade and go to fixation in a population in which all females mate twice provided that $c > 1/(1+2d)$ (Figure 1), i.e. when drive males are sufficiently successful in sperm competition relative to the strength of meiotic drive.

However, this analytical approximation does not accurately predict the fixation criteria for drive mutants that have managed to become fairly common, for example *via* genetic drift or a large influx of migrants carrying X*. Because the complete analytical model is complex, we numerically investigated whether X* was fixed or lost when the population was initiated with a range of X* initial frequencies between 0.01 and 0.99, for a range of values of c and d (Figure 1). We thereby found the minimum initial frequency of X* required for invasion, which predicts the degree to which polyandrous populations are protected against X* (note that X* can invade a monandrous population from any non-zero initial frequency assuming $h = 0$ and $d > 0$ in Model 1).

Figure 1 shows that polyandry causes X* to decline from all starting frequencies if X*Y males are sufficiently disadvantaged in sperm competition relative to the strength of meiotic drive. Therefore, polyandry creates selection against meiotic drivers that reduce the bearer's sperm competitive ability. However, when c was sufficiently high relative to d, X* went to fixation from all starting frequencies. The boundary between the zones of inevitable fixation or inevitable loss of X* was separated by a zone in which the initial frequency of X* determined its fate. This zone was especially large when c was low, i.e. when drive males do not fare well in sperm competition. This result illustrates that fixed levels of polyandry produce positive frequency-dependent selection on X* when carriers are disadvantaged in sperm competition. As X* becomes more common, sperm competition involving only X*Y males becomes increasingly frequent, so the X*

chromosome suffers its sperm competition disadvantage less often.

Acting alone, co-evolving polyandry cannot maintain meiotic drive polymorphism

We next examined whether freely evolving polyandry can maintain polymorphism for meiotic drive, assuming that polyandry has a direct cost ($p > 0$) to females (assuming $p = 0$ generally causes polyandry to fix, simplifying the model to the case in Figure 1).

Figure 2 illustrates three contrasting evolutionary outcomes. In Figure 2A (which assumes no costs to X*X* homozygotes), the meiotic driver went to fixation despite an increase in the frequency of polyandry as X* increased in frequency, leading to the extinction of males. In Figure 2B, we assumed strong costs to X*X* homozygotes, which prevented X* from going to fixation, and also selected for polyandry. The presence of X* resulted in a moderately female-biased sex ratio. In Figure 2C, X* and the polyandry allele oscillate in frequency, since the frequency of one determines the direction of selection on the other.

We then set $p = 0.01$ and varied h, d and c, to determine the effects of the latter parameters on the evolutionary outcome. Each run of the model began with a population in which the sex ratio was even, alleles A and a had frequencies of 0.5, X* had frequency 0.001, and A and X* were in linkage equilibrium. Simulations were terminated after 10^5 generations, and we present the average allele frequencies in the last 10,000 generations (thereby finding the value around which allele frequencies oscillated in cases like Figure 2C).

Figure 3 shows that when $h = 0$ (i.e. X*X* homozygotes had normal fitness), X* typically went to fixation. However for other values of h, polymorphism for drive was possible, with higher h resulting in lower frequencies of X*. As expected, strong meiotic drive (d) and high competitiveness of drive male sperm (c) generally had a positive

effect on the frequency of X*. However, co-evolution between meiotic drive and the polyandry allele (Figure 4) resulted in a more complex picture. For example, one might expect low c to favor the evolution of polyandry, since this condition increases the difference in the proportion of sons produced by polyandrous and monandrous females, all else equal. However, low c also causes X* to be less common, which favors monandry (since polyandry is costly, and there is less need to screen out X* sperm when X* is rare). Consequently, polyandry was especially strongly selected for when drive males were bad, but not too bad, in sperm competition (c = 0.3-0.7; i.e. close to many real-world estimates of drive males' sperm competitive ability; Price and Wedell 2008; Price et al. 2008a). These higher rates of polyandry tended to depress the frequency of X*.

An important result of Model 1 is that we found no evidence that co-evolving polyandry alone is sufficient to maintain genetic polymorphism for drive, because X* always either went to fixation or went extinct assuming h = 0. To confirm that this result was not specific to the limited parameter space chosen for Figures 2 and 3, we searched for parameter values that allowed X* polymorphism to persist by randomly generating 40,000 parameter spaces in which h, d and c varied independently between 0 and 1, and p varied between 0 and 0.2 (initial tests showed that higher p always drove allele A to extinction). Simulations were terminated after 10^5 generations, or when X* reached a frequency of >0.99, and we again recorded average allele frequencies in the last 10,000 generations.

Figures S1 and S2 show the effect of the model's four parameters on the frequency of X* and polyandry respectively. Figure S1 confirms that polymorphism for X* never occurred when h was close to 0 (we additionally ran 10,000 other random parameter spaces all with h = 0 which confirmed this result; not shown), and Figure S2 illustrates that costly polyandry is not selected for if meiotic drive is too weak (low d) or

if the costs of polyandry are too high (high p). Figure S3 shows the effects of effects of the four parameters on the range of the frequency of X* in the last 10,000 generations, showing which parameters values can generate cycling allele frequencies as shown in Figure 2C. Figure S3 suggests that cycles occur when h, c and p are low and d is high. That is, cycling is more likely when X* can quickly spread from low frequencies (high d), and polyandry can rapidly evolve and effectively cause the spread of X* to reverse (low c and p).

Finally, the model found some evidence that when polymorphism for meiotic drive persists, the frequency of drive tends to be negatively correlated with the frequency of polyandry. Figure S4 shows the final frequencies of X* and the polyandry allele for the 40,000 randomly generated parameter spaces shown in Figures S1 and S2. The regression line shows the linear relationship for those parameter spaces for which polyandry and X* had a final mean frequency between 0.01 and 0.09, and the frequency of males was greater than 1%. Although variable values of the model's four parameters created abundant scatter, there was a net negative relationship, likely because polyandry reduces the selective of advantage of X* whenever X* is disadvantaged in sperm competition.

Results of Model 2

The results of Model 2 are summarized in Table 1 and shown graphically in Figures S5-S8. Most of the conclusions are qualitatively identical to Model 1. Strong costs of polyandry (p) disfavored the polyandry allele, allowing X* to spread more readily, and increasing the probability of extinction. The X* chromosome spread more easily if X*Y males were not disadvantaged in sperm competition (c) because more eggs were then fertilized by X*Y males, and probably also because polyandry was not as common when

c was high. Accordingly, high *c* also increased extinction risk. Strong meiotic drive (*d*) greatly increased extinction probability, and had positive effects on X* and polyandry frequency.

Costs to X*X* homozygotes (*h*) again hindered the spread and fixation of X*, reducing the risk of extinction. Importantly, just as in Model 1 we found no evidence that polyandry alone can selectively maintain X* polymorphism: evidence of stabilizing selection on X* was only found when X*X* homozygotes paid a fitness cost ($h > 0$). Specifically, there were no parameter spaces with $h = 0$ in which X* commonly increased from 10% and decreased from 90% initial frequency (Figure S8).

The new parameter *r*, which controlled the rate at which mated males replenished their sperm, had a strong negative effect on extinction probability. This result is expected because when males can rapidly replenish their sperm, female fecundity is less affected by a shortage of males. When *r* was low, polyandry reached higher frequencies, because females derived more benefit from the extra sperm gained by mating twice when their first mate was more often sperm depleted. Likely as a consequence of its negative effect on polyandry frequency, *r* positively affected the frequency of X*.

The other new parameter *m*, which scales the probability that an available female mates at any given male density, had a positive effect on the evolution of polyandry. This result is intuitive because with low *m*, comparatively few females carrying one or two A alleles actually mated twice before reproducing, diminishing the fitness difference between alleles A and a and thus weakening selection on polyandry. Accordingly, the evolution of allele A was highly variable when *m* was low, suggesting drift was strong relative to selection (bottom left, Figure S6). Because multiple mating causes sperm competition, high *m* was associated with somewhat lower frequencies of

X*. Interestingly, higher mating rates were associated with more extinction despite resulting in lower frequencies of X*. This counterintuitive relationship becomes explicable once one notes that all else being equal, the average male is more sperm-depleted when m is high, and females can therefore remain sperm limited even if they hit their mating quota (1 or 2 matings, depending on genotype). The problem of sperm limitation is exacerbated because it selects for polyandry, making sperm even scarcer (for an analogous argument in a different system see Charlat et al. 2007b).

X* tended to be less common when the polyandry allele A was dominant than when it was recessive, presumably because dominance increases the number of females who mate twice for any given A frequency. As a likely consequence, the polyandry allele reached lower frequencies when it was dominant. The effect of allele A's dominance on extinction probability was small and inconsistent.

As in Model 1, the frequency of the polyandry allele negatively predicted the frequency of X* across all non-extinct simulation runs (slope±95% confidence limits: -0.18±0.02; intercept = 0.52±0.02, n = 8409). However, the explanatory effect of polyandry was very weak (R^2 = 0.023), reflecting the plethora of interacting predictors affecting both frequencies.

Discussion

Contrary to our predictions, we found no evidence that co-evolving polyandry provided sufficiently strong negative frequency-dependent selection to maintain polymorphism for an X-linked meiotic drive gene under the present assumptions. However, when the X* chromosome was prevented from reaching fixation by costs to X*X* homozygotes, polyandry had substantial effects on the frequency and evolutionary dynamics of X*. Polyandry was also sometimes able to purge X* if X*Y males were disadvantaged in

sperm competition.

Why didn't polyandry allow stable polymorphism of the driving X?

This result likely stems from variation in the strength and direction of selection on polyandry at different stages of the invasion of the X* chromosome. For any given sex ratio, selection for polyandry is strongest when X and X* are present in exactly equal frequencies in males, because this condition maximizes the chance that polyandrous females will mate with both XY and X*Y males. Therefore, the reduction in the average number of X*-bearing offspring produced by polyandrous females relative to monandrous ones is also maximized. By contrast, when the frequency of X* is close to 0 or 1, polyandry provides weaker benefits (again, for any given sex ratio) because females will usually mate with multiple males of the same type. Selection for polyandry will also tend to be strong at high frequencies of X* relative to lower X* frequencies that are similarly far from 0.5 (e.g. at 0.75 relative to 0.25). This is because higher X* frequencies tend to be associated with a more female-biased population-wide sex ratio; the extra sons produced by polyandrous females therefore tend to have higher reproductive value (Fisher 1930) when X* is common.

Together, these effects mean that the "extra-son" benefits to polyandrous females will be meager until partway through the invasion of the X* chromosome. Although polyandrous females get increasingly more benefits as X* begins to invade, these benefits might start to decline sometime after X* has passed 50% frequency, since polyandrous females then more often fail to also mate with an XY male (this is especially true if the declining abundance of males causes females to mate with fewer males, as in Model 2 and Taylor and Jaenike 2002; 2003). Given that meiotic drivers can spread very quickly, polyandry will often fail to evolve rapidly enough to reach a sufficiently high

level to stop or reverse the spread of X*, assuming that negative frequency-dependent selection on X* from other factors (e.g. a cost to X*X* homozygotes) does not stop or slow its spread. This was true even in Model 2, which introduced an additional benefit to polyandry (extra sperm) that grew more valuable as males became rare.

In short, polyandry needs to be present at high frequencies to stop the spread of X*. A growing invasion of X* does not generate enough selection on polyandry to boost polyandry to high enough frequencies to stop the invasion, and thus unexplained incidences of meiotic drive polymorphism in the wild (see Introduction) seem unlikely to be explained solely by co-evolution with polyandry.

Polyandry can prevent meiotic drive from invading, and influences drive frequency when other factors maintain polymorphism

Although polyandry alone could not protect the X chromosome polymorphism, we found that populations with a high frequency of polyandry are resistant to invasion by X-linked meiotic drivers, provided that drive-carrying males are disadvantaged in sperm competition. This result is similar to that of a previous model of cytoplasmic incompatibility-inducing (CI) *Wolbachia*. Champion de Crespigny et al. (2008) showed that if CI-inducing *Wolbachia* harm the sperm competitive ability of male carriers, *Wolbachia* can be prevented from invading from low initial frequencies. As in our model and those of Taylor and Jaenike (2002; 2003), polyandry can generate positive frequency-dependent selection on *Wolbachia*: once the bacterium becomes sufficiently common, *Wolbachia*-carrying males tend to compete against each other, reducing the importance of selection from their inferior sperm competitive ability against uninfected males (Champion de Crespigny et al. 2008). This suggests that our other results generalize to other kinds of selfish genetic element: for example, it is likely that

coevolution between polyandry and *Wolbachia* prevalence cannot explain puzzling polymorphisms for *Wolbachia* infection under complete maternal transmission or complete CI.

We also found that when costs to X*X* females prevented X* from fixing, costly polyandry was often selectively maintained because it provided benefits in terms of extra sons (which is beneficial in a population containing X*). In these situations, the equilibrium mean frequency of polyandry predicted that of X*. In some cases, polyandry remained at a stable frequency, while in others, polyandry and X* tracked each other in stable cycles. Similar cycles have been found in other models of meiotic drive and drive suppressors (Charlesworth and Hartl 1978; Hall 2004), and of *Wolbachia* causing cytoplasmic incompatibility (Hurst and McVean 1996). Additionally, correlations between polyandry and drive frequency were found in previous models of CI-inducing *Wolbachia* (Champion de Crespigny et al. 2008) and the mouse *t* haplotype (Manser et al. 2011), both of which assumed that males carrying segregation distorters were disadvantaged in sperm competition as in our model. Available theoretical work therefore suggests that observed correlations between polyandry and meiotic drive in natural populations (Pinzone and Dyer 2013; Price et al. 2014) may result from a combination of adaptation in female mating behavior to the local frequency of drive males and negative effects of polyandry on drive allele fitness.

What other factors might stabilize meiotic drive?

Given that polyandry and sperm competition appear unlikely to be the full story, what other factors might be acting to stabilize meiotic drive frequencies in natural populations?

One possibility is that meiotic drivers are strongly affected by the environment, and that seasonal reductions in drive efficacy and/or the fitness of carriers reduce drive frequency to such an extent that drivers cannot spread to fixation over the course of a year. Laboratory estimates of segregation distortion and fitness of carriers may overestimate the selective advantage of meiotic drive, if these parameters are impaired in less benign environments (Feder et al. 1999). Consistent with an effect of climate on the strength of segregation distortion or the relative fitness of drive-bearing individuals, several meiotic drivers appear to be distributed in latitudinal clines, being rarer at high latitudes (Krimbas 1993; Powell 1997; Dyer 2012; Price et al. 2014). This correlation implies that meiotic drive carriers might have reduced survival, fecundity, fertility, mating success and/or drive efficacy in colder climates. However, direct evidence for decreased drive efficacy or fitness of drive-carrying individuals in cooler environments appears to be absent. *D. pseudoobscura* males carrying a driving X chromosome have impaired fertility at high temperatures (Price et al. 2012a), but this finding cannot explain the observed latitudinal cline because the driving X is commoner at warmer latitudes (Price et al. 2014). Wallace (1948) found that *D. pseudoobscura* females homozygous for drive had reduced larval survival, especially at high temperatures, but again this result predicts the opposite latitudinal cline to that which is observed in nature.

Lastly, meiotic drivers might persist in metapopulations, where the drive chromosomes can spread within patches and cause local extinctions. Polymorphism might be maintained at the metapopulation level because patches containing the driver produce fewer migrants, e.g. because females in these patches are more often sperm limited (Taylor and Jaenike 2002; cf. Kokko et al. 2008). However, evidence for local extinctions caused by meiotic drive in natural populations is equivocal (Pinzone and Dyer 2013).

Conclusions

Our models tested whether coevolution with polyandry could provide a sufficiently strong source of negative frequency-dependent selection to prevent the fixation of an X-linked meiotic drive gene that also reduces the sperm competitive ability of male carriers. Although polyandry often became more common after the meiotic driver began to spread, reducing the driver's relative fitness, co-evolving polyandry was never sufficient to prevent the driver from continuing to spread to fixation. However, when we additionally assumed that meiotic drive homozygotes had low fitness, preventing drive fixation, polyandry often had large effects on the frequency and evolutionary dynamics of meiotic drive. We also confirmed that polyandrous populations are more resistant than monandrous populations to invasion by X-linked meiotic drivers that reduce sperm competitive ability.

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Data archiving

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The R script for Model 1 and Matlab script for Model 2 are archived at Dryad (*URL to be added here*).

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Table 1: Summary of the qualitative results of Model 2. See Figures S5-S8 for further details.

Parameter	Effect on X* frequency	Effect on polyandry frequency	Effect on extinction probability
Drive strength (d)	Positive	Positive	Positive
Polyandry cost (p)	Positive	Negative	Positive
Competitiveness of X*Y sperm (c)	Positive	Negative	Positive
Cost to X*X* females (h)	Negative	Inconsistent	Negative
Mating rate (m)	Negative, up to a point	Positive, up to a point	Inconsistent
Sperm replenishment rate (r)	Positive	Negative	Negative
Dominance of polyandry allele	Negative	Negative	Negligible

Figure 1: In a 100% polyandrous population, the invasion of meiotic drive is difficult or impossible if X*Y males are sufficiently disadvantaged in sperm competition, especially when meiotic drive is weak.

The color shows the minimum initial frequency of X* required for X* to invade for each combination of c and d. Darker colors indicate that X* can invade even from a low initial frequency, while white areas indicate that X* would decline from any initial frequency less than one (i.e. a population fixed for X* is invasible by X). Intermediate color shows regions in which X* can invade, but only if it exceeds a certain initial frequency. The line shows the approximate threshold at which X* can invade from any non-zero initial frequency (see Online Supplementary Material). These results assume that all females mate with two males, and $h = 0$.

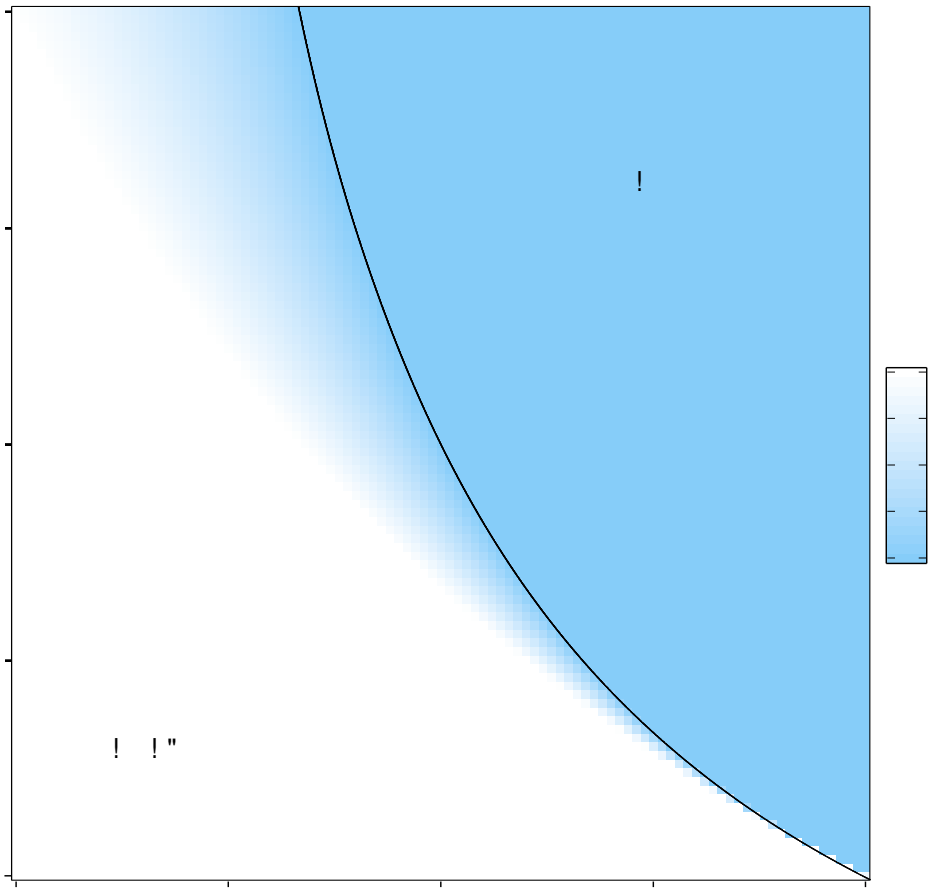

Figure 2: Three contrasting evolutionary outcomes, respectively: fixation of X*, stable polymorphism, and cyclic polymorphism.

In Figure 2A, X* invades from low frequency and goes to fixation, causing extinction of males; the polyandry allele also began to (temporarily) increase in frequency as X* became common, but X* nevertheless continued to fixation. In 2B, strong costs to X*X* homozygotes prevented X* from fixing, and the subsequent increase in the frequency of polyandry affected the equilibrium frequency of X*. Lastly in 2C, stable co-evolutionary cycles of polyandry and X* occurred. We assumed d = 0.9 and starting frequencies of 0.5 for polyandry and 0.001 for X* in all simulation runs.

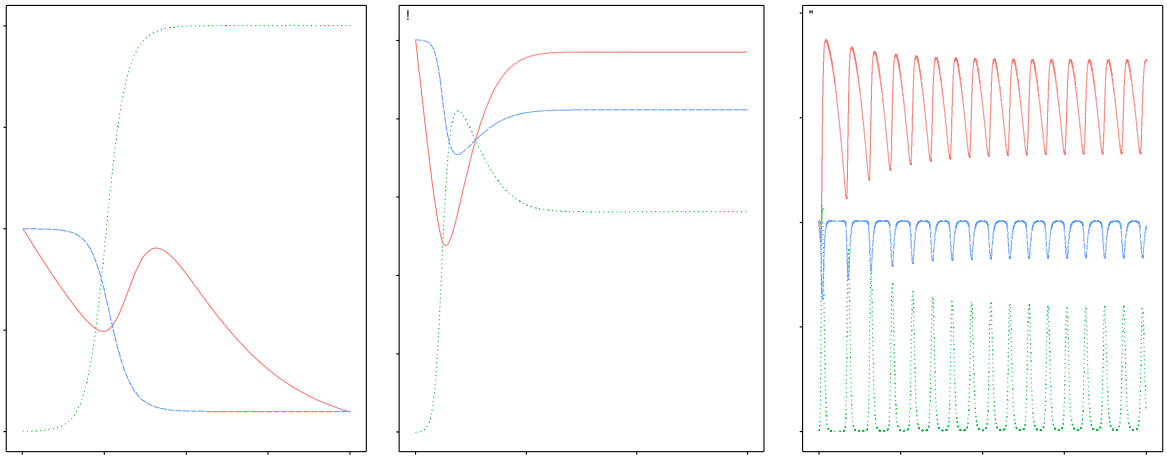

Figure 3: The effect of the parameters c, d, and h on the frequency of X*.

When X*X* homozygotes paid no fitness cost (h = 0), X* fixed for all values of c (assuming d > 0), indicating that co-evolving rates of polyandry alone cannot stop a meiotic driver from invading and fixing. By contrast when h = 0.2, X* only fixed when it did not seriously impact its bearer's sperm competitive ability and meiotic drive was strong; otherwise, X* remained polymorphic. Higher values of h yielded a similar picture, but X* reached lower frequencies due to the reduced fitness of X*X* homozygotes. Grey areas indicate parameter spaces in which the frequency of males dropped below 1%, suggesting that these parameter combinations would lead to extinction in reality. We assumed p = 0.01 and starting frequencies of 0.5 for polyandry and 0.001 for X* in all simulation runs.

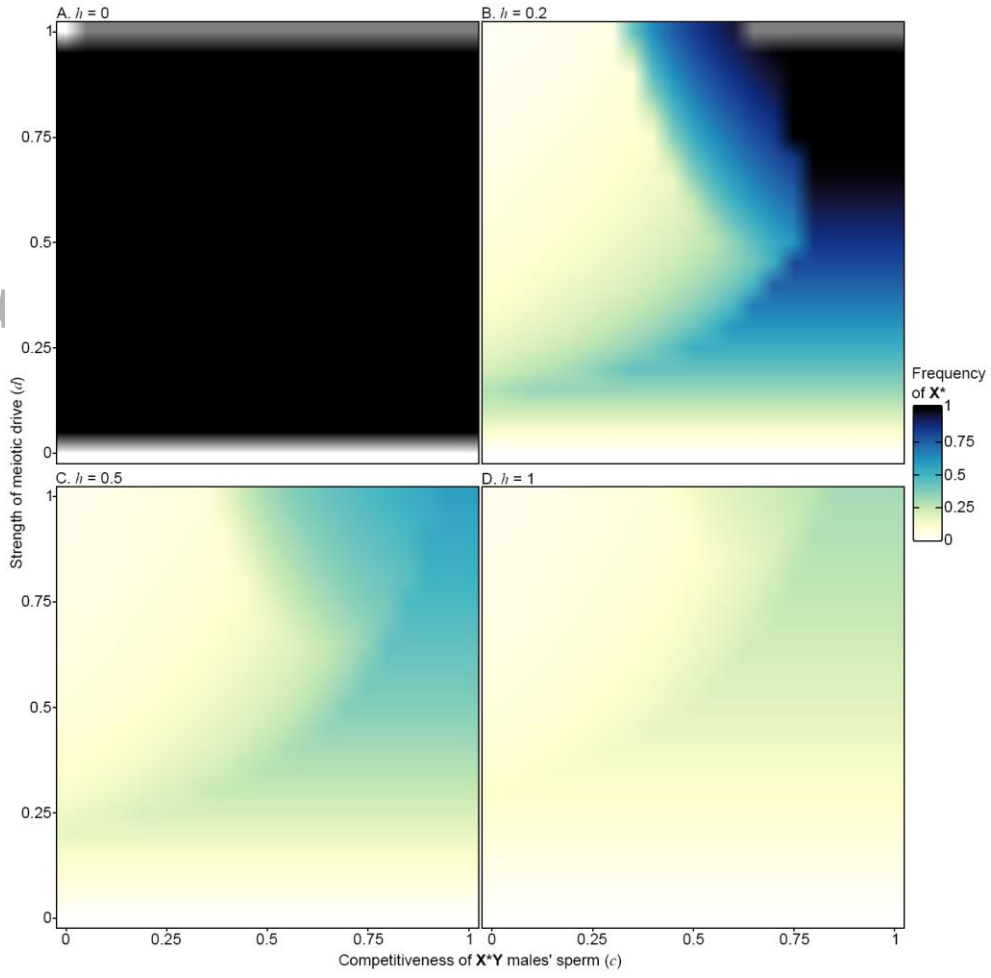

Figure 4: The effect of the parameters *c*, *d*, and *h* on the frequency of polyandry. Polyandry was always lost when $h = 0$, since X* always went to fixation, meaning there were no XY males to favor using sperm competition. For other *h* values, polyandry became most common when *c* was intermediate and *d* was high. Intermediate *h* favored polyandry more than high *h*, since X* was present at lower frequencies if *h* was high. Grey areas indicate parameter spaces in which the frequency of males dropped below 1%, suggesting that these parameter combinations would lead to extinction in reality. We assumed $p = 0.01$ and starting frequencies of 0.5 for polyandry and 0.001 for X* in all simulation runs.